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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/655,598	09/05/2003	Jorg Hager	48506-00009	5726
23767	7590	10/05/2005	EXAMINER	
PRESTON GATES ELLIS & ROUVELAS MEEDS LLP 1735 NEW YORK AVENUE, NW, SUITE 500 WASHINGTON, DC 20006			BABIC, CHRISTOPHER M	
			ART UNIT	PAPER NUMBER
			1637	

DATE MAILED: 10/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/655,598	Applicant(s) HAGER ET AL.	
	Examiner Christopher M. Babic	Art Unit 1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-19 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-19 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. ____. |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>12/5/03</u> | 6) <input type="checkbox"/> Other: ____. |

DETAILED ACTION

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy has been filed in parent Application No. 09/936,299, filed on December 20, 2001.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claim 1-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims 1 and 18, and any claims dependent thereof, are indefinite because Claims 1 and 18 are drawn to a method for the identification, isolation, or separation of identical nucleic acids fragments; however, the final step is for identifying, isolating, or separating the fully-matched heterohybrid fragments. The claims do not set forth the relationship between identical nucleic acids fragments and the fully-matched heterohybrid fragments. Therefore, it is not clear as to whether the claims are intended to be limited to a method of identification, isolation, or separation of identical nucleic

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acids fragments or the identification, isolation, or separation of the fully-matched heterohybrid fragments.

b) Claim 1 is further indefinite because the phrases, "*the* restriction fragments" and "*the* fully-matched heterohybrid fragments", which lacks antecedent basis. Claim 7 is further indefinite because the phrase, "the amplification reaction" lacks antecedent basis. Claim 11 is further indefinite because the phrases, "*the* homoduplexes", "*the* heteroduplexes" and "*the* mismatched heterohybrid fragments" lack antecedent basis. See MPEP 2173.05.

c) Claim 13 is further indefinite because the claim contains information in parentheses, i.e. (blunt-ended) and (homoduplexes). Parentheticals make the claims indefinite because it is unclear whether the information in the parentheses has the same, less, or more weight as the rest of the claim language.

d) Claim 16 is further indefinite because it is not clear as to what material is considered to be "MutS-binding material", this recitation is not an art-recognized term, and furthermore, this recitation is not defined in the specification.

Appropriate correction is required.

Claim Rejections - 35 USC § 102

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

1. Claims 1-7, 10-12, 18, and 19 are rejected under 35 U.S.C. 102(e) as being anticipated by Lin et al. (U.S. 5,871,927).

Regarding Claim 1, Lin et al. disclose a method for the identification, isolation or separation of identical nucleic acid fragments from a mixture of at least two nucleic acid populations (Figure 3; *Especially* Column 8, Lines 52-67), comprising the steps of: a) performing separate digestion of the nucleic acids from said at least two populations with at least one restriction enzyme (Figure 3(a), Step 1; Column 4, Lines 50-52); b) ligating a differently composed adaptor molecule to the restriction fragments (Figure 3(a), Step 1; Column 4, Lines 53-55), wherein said adaptor molecule adds a distinct label for each of said at least two nucleic acid populations (*Especially* Column 8, Lines 52-67) c) hybridizing said ligation products generated in step (b) with each other (Figure 3(a), (b), Step 3; Column 4, Lines 32-36) ; and d) identifying, isolating or separating the identical, fully matched, heterohybrid fragments (Figure 3 (b), Steps 4,5,6; Figure 6 (a-c)).

Regarding Claims 2, 4, and 5, Lin et al. disclose genomic DNA libraries from two sources (Column 4, Lines 19-23).

Regarding Claims 3 and 6, Lin et al. disclose chromosomes (Column 9, Lines 16-35).

Regarding Claim 7, due to the indefiniteness of the claim language (i.e. prior to *the* amplification reaction, please see above rejection) the size selection of restriction fragments can be interpreted to occur at *anytime* during the instant methods. As such,

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it can be interpreted that a size selection occurs during the identifying, isolating or separating of the identical, fully matched, heterohybrid fragments (Figure 3 (b), Steps 4,5,6; Figure 6 (a-c)).

Regarding Claim 10, Lin et al. disclose a unique end sequence at each adaptor molecule (Figure 3(a), (b); *Epecially* Column 8, Lines 52-67).

Regarding Claims 11 and 12, Lin et al. disclose separating the homoduplexes from the heteroduplexes; identifying and eliminating the mismatched heterohybrids; and identifying, isolating or separating the identical heterohybrid fragments (Figure 3 (b), Steps 4,5,6; Figure 6 (a-c); *Epecially* Column 8, Lines 52-67).

Regarding Claims 18 and 19, please refer to the rejection of Claim 1 above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

1. Claims 1-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weissman et al. (U.S. 6,287,825) in view of Lin et al. (U.S. 5,871,927).

Regarding Claim 1, Weissman et al. disclose a method for the identification, isolation, or separation of identical nucleic acid fragments from a mixture of at least two nucleic acid populations, comprising:

- (a) separately digesting the nucleic acids of said populations with at least one restriction enzyme (Column 4, Lines 45-48; Column 7, Lines 45-46; Columns 11-14);
- (b) ligating an adaptor sequence to the restriction fragments (Column 4, Line 57 to Column 5, Line 3; Column 7, Lines 50-53; Columns 11-14);
- (d) hybridizing the products from the different nucleic acid populations with each other (Column 5, Line 57 to Column 6, Line 1; Columns 11-14); and
- (e) identifying, isolating, or separating the fully-matched heterohybrid fragments (Column 6, Lines 2-8; Column 3; Column 11-14).

Weissman et al. does not specifically disclose ligating a differently composed adaptor molecule to each nucleic acid population, wherein the adaptor molecule adds a distinct label.

As stated in the above rejection, Lin et al. disclose a method for the identification, isolation or separation of identical nucleic acid fragments from a mixture of at least two nucleic acid populations (Figure 3; *Especially* Column 8, Lines 52-67) wherein a differently composed adaptor molecule is ligated to the restriction fragments (Figure 3(a), Step 1; Column 4, Lines 53-55), wherein said adaptor molecule adds a distinct label for each of said at least two nucleic acid populations (*Especially* Column 8, Lines 52-67). Specifically, Weissman discloses that when the two distinct adaptor molecules are mismatched by the formation of a heterohybrid, they will produce single-stranded

(i.e. forked) ends (Column 8, Lines 52-56). Weissman et al. disclose digesting perfectly-matched DNAs by Exo III (e.g. blunt-ended), and then single-stranded Exo III created strands by binding said sing-stranded Exo III created strands using a strand specific matrix (Column 1) in order to separate heterohybrids from homohybrids.

Based on the combined teachings of Lin et al. and Weissman et al., one of ordinary skill at the time of invention would have had a reasonable expectation of success practicing the methods of Weissman et al. with the differently composed adaptor molecules discloses by Lin et al. The motivation to do so would have been to digest perfectly-matched DNAs by Exo III (e.g. blunt-ended) in order to separate heterohybrids from homohybrids. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to practice the methods as claimed.

Regarding Claim 2, Weissman teaches the nucleic acid populations comprise human genomic DNA populations (Column 4, Lines 52-56).

Regarding Claims 3-6, Weissman teaches the nucleic acid populations comprise nucleic acid populations from different subjects (or sources) having a common trait of interest and selected chromosomes (e.g., human chromosomes) (Abstract; Columns 1, 3 and 4).

Regarding Claim 7, due to the indefiniteness of the claim language (i.e. prior to *the* amplification reaction, please see above rejection) the size selection of restriction fragments can be interpreted to occur at *anytime* during the instant methods. As such, it can be interpreted that a size selection occurs during the identifying, isolating or

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separating of the identical, fully matched, heterohybrid fragments (Column 6, Lines 2-8; Column 3; Column 11-14).

Regarding Claims 8 and 9, Weissman teaches the adaptors (Y-shaped, dsDNA adaptors comprising at least a 5 base long fragment) can contain restriction endonuclease sites for elimination of homohybrids or heterohybrids, such a recognition site can be GATC, which is specific for mutHL (Columns 1, 3, 7-8; Figure 1(a)).

Regarding Claim 10, Lin et al. disclose a unique end sequence at each adaptor molecule (Figure 3(a), (b); *Especially* Column 8, Lines 52-67).

Regarding Claims 11 and 12, Lin et al. disclose separating the homoduplexes from the heteroduplexes; identifying and eliminating the mismatched heterohybrids; and identifying, isolating or separating the identical heterohybrid fragments (Figure 3 (b), Steps 4,5,6; Figure 6 (a-c); *Especially* Column 8, Lines 52-67).

Regarding Claim 13, Weissman teaches digesting perfectly-matched DNAs by Exo III, and then single-stranded Exo III created strands by binding said sing-stranded Exo III created strands using a strand specific matrix (Column 1).

Regarding Claim 14, Weissman et al. discloses adaptors comprising at least a 5 base long pair (see rejections of Claims 8 and 9 above). Weissman does not specifically disclose a non-complementary relationship between adaptor molecules at the ends in heterohybrids. As stated above, Lin et al. discloses differently composed adaptor molecules wherein they will produce single-stranded molecule (e.g. non-complementary at the end of a heterohybrid (Column 8, Lines 52-56)).

Based on the combined teachings of Lin et al. and Weissman et al., one of ordinary skill at the time of invention would have had a reasonable expectation of success practicing the methods of Weissman et al. with differently composed (e.g. non-complementary) adaptor molecules, wherein the adaptor molecules are non-complementary at least for about 4 nucleotides up to about 10 nucleotides. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to practice the methods as claimed.

Regarding Claims 15 and 17, Weissman teaches the eliminating step occurs via mismatch repair enzymes, such as MutH, MutS and MutL (Column 1-2).

Regarding Claim 16, Weissman teaches incubating the hybridization mixture with MutS and contacting the resulting product with a "MutS-binding material" (Columns 5-6, 11-14).

Regarding Claims 18 and 19, please refer to the rejection of Claim 1 above.


Conclusion

No claims allowed. No claims are free of the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher M. Babic whose telephone number is 571-272-8507. The examiner can normally be reached on Monday-Friday 7:00AM to 4:00PM.

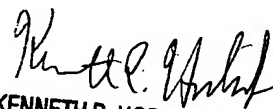
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



9/30/05

Christopher M. Babic
Patent Examiner
AU 1637



KENNETH R. HORLICK, PH.D.
PRIMARY EXAMINER

10/3/05